General Correspondence
Scientific Considerations Related to Developing Follow-on Protein Products

March 15, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 2004N-0355: Scientific Considerations Related to Developing Follow-on Protein Products

Dear Sir/Madam:

Novo Nordisk Inc. appreciates the opportunity to provide comments to the above-captioned Docket on the Scientific Considerations Related to Developing Follow-on Protein Products. Novo Nordisk is a pioneer in the promise of biotechnology and a world leader in diabetes care. The company has the broadest diabetes product portfolio in the industry, including the most advanced products within the area of insulin delivery systems. In addition, Novo Nordisk has a leading position within areas such as hemostasis management, growth hormone therapy, and hormone therapy for women. Novo Nordisk manufactures and markets pharmaceutical products and services that make a significant difference to our patients' lives, the medical profession and society.

Novo Nordisk is concerned that for the first time in the history of biotechnology-derived protein products, the reduction of requirements for safety documentation are being discussed within the U.S. Food and Drug Administration (FDA). Historically, great care has been exercised at the FDA regarding safety risks, and we find no scientific justification for reducing these requirements. Our record demonstrates a very long history of producing safe biological

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medicines for the market, and in upgrading our products, following FDA approval, as new technological developments become available.

While FDA is beginning what we hope will be a transparent and rigorous scientific dialogue, and in the future a legal and regulatory dialogue, we must affirm at the outset that FDA does not currently have the statutory authority to approve a follow-on biotechnology-derived protein product, whether under the Public Health Service Act or the Food, Drug, and Cosmetic Act (FDCA). Accordingly, Congress must ultimately provide the authority for FDA to proceed.

General comments on the approval of follow-on biotechnology-derived protein products

Neither of the approval pathways established under the Hatch-Waxman Amendments to the FDCA -- neither the abbreviated new drug application (ANDA) process under FDCA section 505(j), nor the "paper NDA" provisions under section 505(b)(2) -- are applicable to biotechnology-derived protein products. These approval pathways were specifically designed for traditional small-molecule drug products, and fail to take account of the uniqueness and manufacturing complexities of biological products. Because of the difficulties inherent in characterizing the identity and structure of biotechnology-derived protein products, the specific manufacturing and control processes used to create those products largely determine their clinical attributes, such as safety and effectiveness.[1] Therefore, the safety and effectiveness data submitted by the original manufacturer cannot be meaningfully relied upon in isolation from the manufacturing and control data submitted by that manufacturer. These manufacturing data are, however, trade secret and confidential commercial information, and constitute the intellectual property of the innovator. Novo Nordisk believes that no future regulatory process for biotechnology-derived protein products may rely, directly or indirectly, on another company's trade secret and confidential commercial data and information. Rather, any FDA approval of such follow-on products would require a full complement of preclinical, clinical and manufacturing data. Any approval process for follow-on biotechnology-derived products must be developed in accordance with the following principles:

- FDA cannot use or disclose an innovator's trade secret information to the public or another company. Under the current state of scientific knowledge, it would be extremely difficult – if not impossible – for FDA to determine that a follow-on biotechnology-derived protein product was the "same as" the innovator's product. To the extent FDA could make such a determination, however, reference to the innovator's safety and effectiveness information alone would not be sufficient. To approve the follow-on, the agency would be required to rely on protected trade secret data and confidential commercial information about the manufacturing processes used to create the innovator product. Innovators' trade secret and confidential commercial manufacturing data are, however, protected from such use under Federal laws including the FDCA and its

[1] *See* FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products ("April 1996 Comparability Guidance").

implementing regulations; the Federal Trade Secrets Act; the Freedom of Information Act; and the 5th Amendment of the U.S. Constitution.

- Manufacturing processes for biologics are extremely complex and unique – from cell line to product. Therefore, a submission for approval of any biotechnology-derived protein product to FDA must contain a complete chemistry, manufacturing and control (CMC) section without relying, directly or indirectly, on the innovator's trade secrets or confidential proprietary information.
- Comparisons based on testing and characterization of active substance and finished product are not sufficient to establish the safety and efficacy of a biotechnology-derived protein product. Preclinical and clinical studies are necessary to establish the safety and efficacy of these products.
- The preclinical safety documentation must include extensive preclinical studies to support first clinical dosing, and should also cover all indications included in the application. In addition, there must be sufficient animal data to confirm biological activity, mechanism of action, and efficacy, where appropriate.
- Biotechnology-derived protein products are not all alike, and therefore clinical programs will to some extent need to be designed on a case-by-case basis. However, all clinical development programs must have a full complement of the following components:
    - Safety data, including long-term immunogenicity studies.
    - PK/PD data.
    - Clinical data to confirm the product's efficacy in each indication. The design of clinical studies including duration and number of patients must be based on scientific and statistical considerations.
    - Pharmacovigilance plan.

Clarifications on the 1998 priority review of GlucaGen®

Novo Nordisk believes that the 505(b)(2) approval mechanism should continue to be utilized only for chemically-derived drugs, and only where manufacturing data or safety and efficacy data that the applicant wishes to rely on are available for submission, as originally intended by Congress under the Hatch-Waxman Amendments of 1984. During the February 14 – 16, 2005 FDA/DIA workshop, FDA referenced the approval of GlucaGen® as an example of a biologic approved under 505(b)(2) of the FDCA. The approval of GlucaGen® warrants additional clarification, as the 505(b)(2) pathway was appropriate in that case only due to extraordinary circumstances.

GlucaGen®, the *first* recombinant (r-DNA) form of glucagon, was approved in the U.S. in June 1998 (submitted in September 1997) for the treatment of severe hypoglycemia and as a diagnostic aid for gastrointestinal radiologic examination. In 1997, a non-r-DNA product, known as Glucagon USP (derived from purified beef and pork pancreas) was a sole source in the U.S. Because of an urgent need to avoid the potential for transmissible agents in drug products derived from animal sources, discussions between FDA and Novo Nordisk resulted in an agreement to utilize a modified 505(b)(2) application mechanism. Priority review for approval of GlucaGen® was granted on October 22, 1997.

At the time of submission for GlucaGen®, Novo Nordisk possessed significant experience with its own non-r-DNA glucagon product of pancreatic origin (Glucagon Novo 1 mg), which the company produced and marketed in Europe, Japan, and other industrialized nations for 20 years. In addition to our extensive scientific and manufacturing history with the pancreatic glucagon product, Novo Nordisk produced and marketed the r-DNA form of glucagon, GlucaGen®, in Europe, Japan, and other industrialized nations for five years prior to our submission to FDA, resulting in a wealth of first-hand clinical, safety and post-marketing data. Moreover, Novo Nordisk also included publicly available literature, as well as a full CMC package, in its application. This exhaustive information and data enabled Novo Nordisk to receive priority approval without relying, directly or indirectly, on another manufacturer's confidential, protected trade secret and commercial information.

Conclusion

Novo Nordisk is concerned that the reduction of requirements for safety documentation in the approval of biotechnology-derived protein products is under consideration within the FDA. Due to an urgent need to protect public health, this unique approval situation surrounding GlucaGen® cannot and should not be used as a rationale for future regulatory processes. In addition, Novo Nordisk urges FDA to refrain from disclosing, directly or indirectly, trade secret and confidential commercial information and data that Novo Nordisk and other innovators have entrusted to the agency under longstanding legal guarantees of confidentiality. It is critical for the future of our industry that FDA take the appropriate steps to safeguard this valuable information.

Sincerely,
NOVO NORDISK INC.

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General Counsel

Mary Ann McElligott
Associate Vice President
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